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| 13. SUPPLEMENTARY NOTES | | | | | |
| 14. ABSTRACT Recent animal research suggests that reactivation (retrieval) of a consolidated memory can return it to a labile state from which it must be restabilized in order to persist. This stabilization process has been termed "reconsolidation," and various behavioral and pharmacologic interventions have been found to modify or block it. The aim of this project is to create an experimental assay in the form of an optimal Pavlovian differential fear conditioning paradigm, within which the relative strengths of various novel pharmacological and behavioral, reconsolidation-blocking interventions can be tested. Thus far, we have successfully implemented the procedure, and are meeting or nearly meeting our recruitment goals. We have validated the novel fear conditioning paradigm by demonstrating differential conditioning in participants. Data collected to date have been subjected to preliminary analysis. Although several interesting trends are present, it is too early to draw conclusions. Subjects are continuing to be studied. | | | | | |
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1. INTRODUCTION

The aim of this project is to create an experimental assay in the form of an optimal Pavlovian differential fear conditioning paradigm. Animal research suggests that reactivation (retrieval) of a consolidated memory can return it to a labile state from which it must be restabilized in order to persist. This stabilization process has been termed “reconsolidation,” and various pharmacological (e.g., propranolol) and non-pharmacological (e.g., delayed extinction) interventions can block it. This ability offers novel therapeutic possibilities for PTSD. However, prior studies (Kindt et al. 2009; Schiller et al. 2010) have encountered a floor effect, such that tested interventions resulted in total abolition of the fear memory. A floor effect precludes the ability to compare the *relative* efficacies of distinct interventions. Therefore, the sub-aim in this work is to design a new experimental protocol that is free of floor effects. Specifically, we will test the following modifications to existing experimental designs: 1) use of a more highly “prepared” (i.e., danger-signaling) conditioned stimulus (CS); 2) recruitment of more sensitive subjects; 3) selection of only subjects who acquire strong conditioned responses (CRs) during conditioning for further participation, and 4) use of additional probes for the presence of the latent CR, viz., renewal and savings in addition to spontaneous recovery and reinstatement.

To avoid the floor effect, we are using a highly “prepared” conditioned stimuli (in this case, high definition video of crawling tarantulas), meaning one that has been shown to more readily and strongly associate with the unconditioned stimulus. We will also recruit subjects who are more likely to be sensitive to the tarantula stimuli, and of those select only subjects who demonstrate conditioning on the first visit.

The study design randomizes subjects into either of two groups. One receives a drug intervention (propranolol), while the other receives a non-drug/behavioral intervention.

2. Body

2.1 Human Work

2.1.1 Massachusetts General Hospital (MGH)

Informed by recent research from other labs demonstrating pharmacological (Kindt et al. 2009) and non-drug (Schiller et al. 2010) post-reactivation interventions, as well as our own prior research (Brunet et al., 2008) with propranolol and PTSD patients, we conducted an open label study examining the relative efficacies of pharmacological and non-drug interventions within a fear conditioning paradigm. At the time of the last quarterly report, we had successfully recruited 17 subjects, 14 of which ultimately completed participation. This fell short of our recruitment goal outlined in the Statement of Work. Since that time we have increased our rate of recruitment to the desired level of 2 subjects per week. As of January 19th, 2012, we had recruited an additional 15 subjects, with 12 completing the initial three visits. Thus, during the 01 year, we recruited 32 total subjects, resulting in 6 drop outs and 26 completions.

An additional 2 subjects are in various stages of participation, while 5 subjects are being actively recruited.

2.1.1.1 Progress to date

As stated above, during the 01 year, 26 participants completed the initial 3 visits of the study protocol. Of those due for a follow-up ($n=12$), all returned and completed the 4th visit. Overall, a total of 75 participants have been screened since study startup. An additional 2 subjects are currently participating, and 5 others are in various stages of being recruited.

Aside from recruitment, we achieved the following research goals during year 01:

- Developed custom, high-definition video of spiders to serve as stimuli
- Developed custom software to run the protocol
- Adapted the existing psychophysiological equipment to accommodate and incorporate the new protocol

2.1.1.2 Results.

Skin conductance responses during the 3-session fear conditioning procedure are presented in Figure 1. As can be seen in the left-half of the figure (Day 1), subjects showed strong differential conditioning to the to-be-reactivated conditioned stimulus (CS+R, paired with a mild shock UCS) vs. the CS- (CS not paired with the UCS; $F(1,210)=43.97$, $p<.001$) as well as to the not-to-be-reactivated conditioned stimulus (CS+N, paired with a mild shock UCS) vs. CS- ($F(1,210)=94.85$, $p<.001$).

Skin conductance responses following the fear-reinstatement procedure are depicted in the right-most side of Figure 1 (Day 3). As can be seen, following fear reinstatement trials (mild shock presented alone 3 times), SC reactivity to the previously reactivated and treated fear stimulus (CS+R) was substantially diminished, such that there was no difference in reactivity to the CS+ vs. CS- trials ($F(1,266)<1$, $p=.97$). In contrast, subjects showed a significant differential SC response to the CS+N vs. CS- trials ($F(1,266)=8.54$, $p<.004$), indicating a persistent fear response to the non-reactivated and untreated CS+ (CS+N). These preliminary results demonstrate our ability to establish a conditioned fear response to a "biologically prepared" stimulus (i.e., video clip of a moving spider) and selectively reduce this conditioned response by blocking memory re-consolidation with propranolol.

3. Key Research Accomplishments

3.4. Progress in studying normal humans in an open label study, examining the efficacy of post-activation propranolol and non-drug interventions as potential modes of blocking reconsolidation (Status: study underway).

3.4.1 Continuing recruitment of participants at a rate of approximately 2 per week

3.4.2 Development and integration of study stimuli and software

3.4.3 Confirmation that the paradigm establishes differential conditioning, and that the resulting conditioned response can be selectively reduced by blocking re-consolidation with

propranolol.

4. Reportable Outcomes

N/A

5. Conclusions

Results are preliminary. However, at present the data suggest that we are able to establish differential conditioning to the biologically prepared stimuli, and subsequently reduce the reinstated conditioned response with post-reactivation propranolol. We intend to continue recruiting subjects and following the current protocol.

6. References

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Kindt M, Soeter M, Vervliet B. Beyond extinction: erasing human fear responses and preventing the return of fear. *Nat Neurosci* 2009;12:256-258.

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7. Appendices (figures of the data)

FIGURE 1:

